

REMARKS

Upon entry of the present amendment, claims 16, 19, 20, 25 and 26 will be amended, whereby claims 16, 19, 20, 25 and 26 will remain pending.

By the amendment herein, claim 16 has been amended to remove an extraneous parenthesis. Claims 16, 25 and 26 have been amended to more explicitly include the term "composition". Moreover, claims 19 and 20 have been amended to remove Markush language.

Moreover, the specification and claims have been amended to include the more conventional spelling of *Cistus monspeliensis* L. In this regard, Applicants note that the U.S. Patent No. 6,313,214 to Tamai, which is utilized in the rejection of Applicants' claims, discloses the same "*Cistus monspeliensis* L." as recited by Applicants. See, for example, Tamai, column 2, lines 44; and column 3, line 60.

However, it is noted that the more conventional academic spelling is *Cistus monspeliensis* L. and the specification and claims have been amended to include this academic spelling. For example, reference is made to <http://commons.wikimedia.org/wiki/Cistus> and http://commons.wikimedia.org/wiki/Cistus_monspeliensis, and downloads from these websites dated June 29, 2008 are submitted herewith.

Reconsideration of the restriction requirement, the objection and the rejection of record, and allowance of the application in view of the following remarks are respectfully requested.

Discussion Of Telephone Interview

Applicants hereby confirm a March 18, 2008 telephone interview between the Examiner and Applicants' representative Arnold Turk. During this telephone interview, the Examiner

indicated that the Restriction Requirement made in the Office Action mailed November 27, 2007 was erroneous, and indicated that it would be revised. To advance prosecution of the application, Applicants' representative indicated that the species *Glycyrrhiza glabra* extract was elected with traverse.

Election With Traverse

Applicants hereby confirm the election of the species *Glycyrrhiza glabra* extract, and submit that, as noted in the Office Action, claims 16, 19, 20, 25 and 26 are generic, and that claims 16, 19, 20, 25 and 26 are readable on the elected species.

Notwithstanding the election of species *Glycyrrhiza glabra* extract in order to be responsive to the Restriction Requirement, Applicants respectfully traverse the requirement for restriction.

Applicants submit that the assertion of lack of unity is without appropriate basis as the assertion does not establish, as required by 37 C.F.R. 1.475 (a), that the there is not a technical relationship among those inventions involving one or more of the same or corresponding special technical features, with the expression "special technical features" meaning those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Therefore, the restriction requirement is not proper, and should be withdrawn.

Claim of Foreign Priority

Applicants express appreciation for the acknowledgement of the claim of foreign priority as well as receipt of the certified copy of the priority application in this national stage application.

Information Disclosure Statements

Applicants also express appreciation for the Examiner's confirmation of consideration of Applicants' Information Disclosure Statements, filed January 31, 2006, June 28, 2006, October 22, 2006, and March 13, 2007, by including initialed copies the Forms PTO-1449 with the Office Action.

Response To Objection To Claim 16

In response to the objection to claim 16 because at the beginning of line 3 there is an erroneous ")", Applicants have amended claim 16 to remove this erroneous parenthesis.

Accordingly, this ground of objection should be withdrawn.

Response To Rejection Under 35 U.S.C.112, Second Paragraph

Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

The rejection contends that claims 19 and 20 are indefinite due to improper Markush language.

In response, Applicants have amended claims 19 and 20 in the manner discussed above. Accordingly, this ground of rejection should be withdrawn.

Claims 19 and 20 are also asserted to be indefinite because the identity of "Cistus monoperiensis" is asserted to be indefinite. The rejection contends that a search of this plant species did not produce any results other than Applicant's own work.

In response, Applicants note that the rejection refers to Applicants' own work, but does not explain what is intended by this assertion. Moreover, as discussed above, the claims (and specification) have been amended to include the more conventional spelling of "*Cistus monspeliensis* L." Accordingly, this ground rejection should be withdrawn.

Claim 20 is also asserted to be indefinite because it is asserted that it is unclear what the claim is attempting to claim. In response, the claim 20 has been amended to explicitly recite that the composition is formed from one, or two or more extracts, containing said compound represented by formula (1), selected from *Cistus ladaniferus* L., *Cistus creticus* L., *Cistus monoperiensis* *monspeliensis* L. and *Cistus salvifolius*.

Accordingly, the rejections under 35 U.S.C. 112, second paragraph, should be withdrawn.

Response To Rejection Under 35 U.S.C. 112, First Paragraph

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as it is asserted that the claims contain subject matter which is not enabled apparently because these claims recite *Cistus monoperiensis* L.

In response and as discussed above, the claims (and specification) have been amended to include the more conventional spelling of "*Cistus monspeliensis* L." Moreover, Applicants submit that this plant is known and obtainable, and is readily available to the public, as discussed above.

Therefore, the enablement rejection should be withdrawn.

Response To Obviousness Rejection

Claims 16, 19, 20, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamai, U.S. Patent No. 6,313,214 and Hadas, U.S. Patent No. 5,609,875.

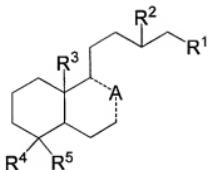
The rejection asserts that Tamai teaches the compounds claimed as ingredient (A), formula 1, and that these compounds can be extracted from the plants claimed in claims 19 and 20. The rejection contends that Tamai teaches that these compounds are used to treat skin ageing by lightening the skin, but that Tamai does not teach using Glycyrrhiza glabra extract in the composition.

The rejection asserts that Hadas teaches using Glycyrrhiza glabra extract for lightening the skin.

The rejection concludes that, "It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose."

The rejection further points to data at pages 62 and 63 (apparently pages 65 and 66) of Applicants' specification and notes that the specification states that this data shows synergistic results for the combination of ingredient (a) and G. Glabra extract. However, the rejection contends that these results are not considered to show synergistic results. The rejection contends that the results in Table 2-1 appear to be qualitative judgments rather than quantifiable date, and that the burden is on the Applicants to show how offered data is of statistical significance.

In response to this ground of rejection, Applicants submit that one having ordinary skill in the art would not have arrived at an external preparation composition for skin, as recited in Applicants' independent claim 16, by combining (A) one, or two or more compounds represented by formula (1) below:



in formula (1), R¹ represents -CH₂OH or COOR⁶, R⁶ represents hydrogen, a lower alkyl group having the number of carbon atoms of 1 to 3, or a cation capable of forming a salt with COO⁻, each of R² to R⁵ independently represents a hydrogen atom or methyl group, and ⋯A⋯ represents =C(CH₃)-, -C(CH₃)=, -C(=CH₂)-, -CH(CH₃)- or -C(OH)(CH₃)-; and (B) one, or two or more medicinal ingredients selected from the group consisting of *Glycyrrhiza glabra* extract, *Coix lachryma-jobi* extract, blackcurrant fruit extract, *Inula britannica* extract, cranberry fruit extract, *Mucuna birdwoodiana* extract, cactus extract, *Momordica grosvenorii* extract, and astaxanthin and its derivatives. Moreover, Applicants submit that the compositions recited by Applicants comprising the recited ingredients (A) and (B) exhibit superior effects beyond the expectation of those skilled in the art at the time the invention was made.

Experimental tests shown below were carried out on behalf of the Applicants to clarify the superior effects of the compositions as recited by Applicants. Applicants note that the methods shown below and the data of the examples and their preparation methods are the same as those described in the description of the international application as filed, as see the specification beginning at page 30, Example 3.

(i) Melanin Production Suppression and Cell Survival Rate Test based on Cell Culture

Murine cultured B16 melanoma cells were used. An appropriate quantity of a 10% FBS-containing MEM medium was placed in two 6-well plates, the B16 melanoma cells were seeded therein and allowed to stand at 37°C under a carbon dioxide concentration of 5 vol%. Next day,

each preparation sample was added and mixed therewith so as to adjust the final concentrations of the *Cistus ladaniferus* L. extract obtained in Example 1 (See Applicants' specification at pages 26), and labdenic acids and methyl esters and ethyl esters thereof obtained in Examples 2 to 5 (See Applicants' specification at pages 26-40) or 10 $\mu\text{g}/\text{mL}$, and of each whitening agent, *Glycyrrhiza glabra* extract to 0.5 $\mu\text{g}/\text{mL}$ as a dry solid content, or cranberry fruit extract, *Mucuna birdwoodiana* extract, cactus extract, *Inula britannica* extract, blackcurrant fruit extract, *Coix lachryma-jobi* extract or *Momordica grosvenorii* extract to 25 $\mu\text{g}/\text{mL}$ as a dry solid content or astaxanthin to 25 $\mu\text{g}/\text{mL}$. The concentration of each whitening agent was decided so that the cell survival rate was equal to or more than 90%. The medium was exchanged on the fifth day of culture, and the preparation sample was added again. The medium was removed next day, the cells were collected from one plate after washing them using a phosphate buffer (pH7), and degree of whitening of the cultured B16 melanoma cells was evaluated according to the criteria shown below.

As comparative examples, the combinations with 20 $\mu\text{g}/\text{mL}$ of kojic acid, 50 $\mu\text{g}/\text{mL}$ of ellagic acid and 12.5 $\mu\text{g}/\text{mL}$ of arbutin, all of which are known whitening agents, as disclosed in Tamai, were examined in the same manner. The concentration of each whitening agent was decided so that the cell survival rate was equal to or more than 90%.

Coixlachryma-jobi extract was obtained by adding 100 mL of a 70 vol% water-containing ethanol to 10 g of *Coixlachryma-jobi* (Japan Pharmacopoeia), carrying out extraction at room temperature for 3 days, and by filtering the mixture. Dry solid content of the *Coixlachryma-jobi* extract was found to be 0.8%.

Regarding other extracts or the like used in the test, their origins such as names of the manufacturing companies and the number of the preparation methods are shown in Table No. 1

(Criteria for Judgment)

++: distinctively stronger whiteness over the reference;

+: apparently stronger whiteness over the reference;

±: slightly stronger whiteness over the reference; and

-: remained unchanged black.

On the other plate, the cells were fixed with formalin, and dyed by adding an 1% crystal violet solution. Cell survival rates for the individual sample concentrations were measured using a monocellator (product of Olympus Corporation). All of the samples showed the cell survival rate not less than 90%. The results of the external preparation for skin falling within the scope of Applicants' claims, Sample Nos. 1-9, are shown in Table No. 1; and the results of the comparative examples, Sample Nos. 10-12, are shown in Table No. 2.

(ii) Cell Activation Test

The cell activation test and evaluation of each sample was carried out in the same manner as "Example 32: Cell Activation Test based on Cell Culture" described on page 67 of Applicants' specification.

As a comparative example, a composition formed of the combination of the compound of the formula (1) and glycolic acid, which is a known cell activation agent, was prepared and evaluated in the same manner.

The results are shown in Table No. 3.

Table No. 1

Evaluation	Sample	Sample No.	1	2	3	4	5	6	7	8	9
		Ingredient	astaxanthin	Glycyrrhiza glabra extract*	cranberry fruit extract*	Mucuna birdwoodian extract*	cactus extract*	Inula britannica extract*	blackcurrant fruit extract*	Coix lachryma-jobi extract*	Monordica groeneworii extract*
		Origin	from Itano Co., LTD.	from MARUZEN PHARMACEUTICALS CO.,LTD.	Example 25	Example 26	Example 29	Example 24	Example 23	—	Example 30
		Final concentration ($\mu\text{g}/\text{mL}$)	25	0.5	25	25	25	25	25	25	25
	<i>Cistus ladaniferus</i> <td>10</td> <td>++</td> <td>++</td> <td>++</td> <td>++</td> <td>++</td> <td>++</td> <td>++</td> <td>++</td> <td>++</td>	10	++	++	++	++	++	++	++	++	++
	Acid mixture	5	++	++	++	++ ^t	++	++	++	++	++
	Methyl ester mixture	5	++	++	++	++	++	++	++	++	++
	Ethyl ester mixture	5	++	++	++	++	++	++	++	++	++
Degree of whiteness	Compound 1	5	++	++	++	++	++	++	++	++	++
	Compound 4	5	++	++	++	++	++	++	++	++	++
	Compound 7	5	++	++	++	++	++	++	++	++	++

* dry solid content

Table No. 2

Evaluation	Sample	Sample No.	10	11	12
		Ingredient	kojic acid	ellagic acid	arbutin
		Origin	from Tokyo Chemical Industry Co., Ltd.	from Tokyo Chemical Industry Co., Ltd.	from Tokyo Chemical Industry Co., Ltd.
		Final concentration (μ g/mL)	25	50	12.5
Degree of whiteness	Cistus ladaniferus L. Extract	10	+	+	+
	Acid mixture	5	+	+	+
	Methylester mixture	5	+	+	+
	Ethylester mixture	5	+	+	+
	Compound 1	5	+	+	+
	Compound 4	5	+	+	+
	Compound 7	5	+	+	+

Table No. 3

Evaluation	Sample	Sample No.	13	14	15
		Ingredient	cactus extract*	astaxanthin	glycolic acid
		Origin	Example 29	from SIGMA	from Tokyo Chemical Industry Co., Ltd.
		Final concentration ($\mu\text{g/mL}$)	1	5	5
Cell-activation rate (%)	Cistus ladaniferus L. Extract	10	230	190	155
	Acid mixture	5	290	215	165
	Methylester mixture	5	280	205	160
	Ethylester mixture	5	305	220	160
	Compound 1	5	300	225	165
	Compound 4	5	310	240	170
	Compound 7	5	315	245	170

* dry solid content

Sample Nos. 10-12 are the same as compositions described in the Example section of Tamai, Text Example 2, at column 9, beginning at the top of the column, comprising a compound represented by the formula (1) and, as a whitening agent, kojic acid, arbutin, and ellagic acid respectively. Thus, Sample Nos. 10-12 fall within the scope of Tamai. From the results shown in Table Nos. 1 and 2, it is understandable that all of Sample Nos. 1-9, falling within the scope of Applicants' claims (including the elected species of *Glycyrrhiza glabra* extract), shown in Table No. 1, exhibit superior effect in suppressing melanin production compared to Sample Nos. 10-12 according to Tamai shown in Table No. 2.

Thus, the compositions disclosed by Applicants are not taught or suggested by either of Tamai and Hadas. Moreover, Applicants' recited compositions exhibit superior effects compared to the compositions disclosed in Tamai. Applicants submit that one having ordinary

skill in the art would not have expected the superior effect of the present invention at the time of filing of their application.

Still further, attention is directed to Table No. 3, wherein Sample No. 15 shown therein is according to Tamai. From the results shown in Table No. 3, it is understood that both of Sample Nos. 13 and 14, falling within the scope of Applicants' claims, exhibited superior effect in cell activation action compared to Sample No. 15. The anti-aging external preparation for skin as set forth in Applicants' claims exhibits superior effect compared to the compositions disclosed in Tamai. One having ordinary skill in the art would have not have expected the superior effect of the present invention.

If the Examiner would like any of the information present herein in the form of a Declaration, the Examiner is requested to contact the undersigned to discuss the submission of a Declaration.

Moreover, if for the sake of argument a *prima facie* case of obviousness is present, Applicants' showing of unexpected results establishes patentability of Applicants' claims subject matter. Accordingly, the rejection of record should be withdrawn.

Accordingly, Applicants submit that Applicants' compositions recited in claims 16, 19 and 20, and methods recited in claims 25 and 26 are patentable over the prior art of record, and the rejection should be withdrawn.

CONCLUSION

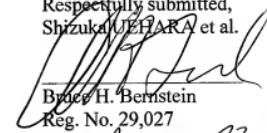
For the reasons discussed above, it is respectfully submitted that the Examiner's requirement for restriction is improper and should be withdrawn.

Withdrawal of the requirement for the restriction with the examination of all claims pending in this application is respectfully requested.

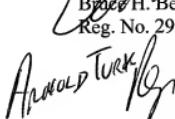
Favorable consideration with early allowance of the pending claims is most earnestly requested.

If the Examiner has any questions, or wishes to discuss this matter, please call the undersigned at the telephone number indicated below.

Respectfully submitted,
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